

# **Rec'd PCT/PTO 05** SEP 2001

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Nicholas Bachynsky Woodie Roy

Serial No.: 09/744622 (PCT/US99/16940)

Filed: January 26, 2001

For: CHEMICALLY INDUCED

INTRACELLULAR HYPERTHERMIA

RECEIVED

19 SEP 2001

Anternational Division

Examiner: Unassigned

Group Art Unit: Unknown

Atty. Docket: P01615US1 / 09805783

(U.S. Nat'l. Phase)

## **PETITION UNDER 37 CFR 1.47**

Texas Pharmaceuticals, Inc., assignee of the whole interest in the above-referenced invention, respectfully requests that a declaration signed by assignee be accepted in fulfillment of the Notification of Missing Parts Requirements Under 35 U.S.C. 371 in the United States Designated/Elected Office mailed March 5, 2001. The inventors in the above-referenced application have refused to execute a current Declaration in this application after numerous attempts have been made to have them execute one, although they signed one when the provisional application on which the above-identified application is based was filed. Their refusal apparently stems from a dispute between them and the owner of the application, Texas Pharmaceuticals, Inc.. The inventors executed assignments of the invention to Texas Pharmaceuticals, Inc., copies of which are attached as Exhibit A. The earlier signed declaration is attached as Exhibit B. The general attorney for Texas Pharmaceuticals, Inc. advised the undersigned that the inventors would not sign a current declaration and refused to accept letters by certified mail.

Thus, in order to preserve the rights of the parties and to prevent irreparable harm by allowing the application to become abandoned, it is necessary to accept a declaration signed by

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the assignee of the application, Texas Pharmaceuticals, Inc. prior to the expiration of the time period set for submission.

The last known addresses of the inventors are:

Nicholas Bachynsky 5944 Coral Ridge Drive, Suite No. 202 Coral Springs, FL 33076

Woodie Roy 5944 Coral Ridge Drive, Suite No. 202 Coral Springs, FL 33076

Please charge the deposit account of Fulbright & Jaworski LLP, Account No. 06-2375, for the petition fee of \$130.00 and any additional fees that may be necessary.

09/13/2001 SNAJARRO 00000073 062375

01 FC:122

130.00 CH

Paul E. Krieger

Registration No.: 25,886

Respectfully submitted,

Data

FULBRIGHT & JAWORSKI L.L.P.

1301 McKinney, Suite 5100

Houston, Texas 77010-3095

Phone: (713) 651-7732 FAX: (713) 651-5246



# Exhibit 1



I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to BOX: PCT; Assistant Commissioner for Patents, Washington, D.C. 20231 on 17 July 2000

Colby S. Delgado

OSignature

Date

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

§

Applicant:

Nicholas Bachynsky

Woodie Roy

Serial No.: PCT/US99/16940

Filed: July 27, 1999

For: CHEMICALLY INDUCED INTRA-

CELLULAR HYPERTHERMIA

Atty. Docket: P01615WO0 / 09805783

Box: PCT

Assistant Commissioner for Patents

Washington, D.C. 20231

## TRANSMITTAL LETTER

Dear Sir:

Enclosed for filing in the above-identified international application are the following:

- Assignment executed by Nicholas Bachynsky on March 4, 1998 and Recordation Form Coversheet;
- Assignment executed by Woodie Roy on July 21, 1998 and Recordation Form Coversheet;
- Check in the amount of \$80.00; and
- Return postcard.

Please charge any additional fees and/or credits to the deposit account of Fulbright & Jaworski L.L.P. under account number 06-2375/09805783, from which the undersigned is authorized to draw. A duplicate of this letter is enclosed for accounting purposes.

Respectfully submitted,

Date:  $\int \int u dt dt = \int \int u dt dt$ 

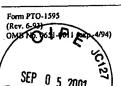
David L. Fox, Ph.D.

Reg. No. 40,612

FULBRIGHT & JAWORSKI L.L.P.

1301 McKinney, Suite 5100 Houston, Texas 77010-3095

Phone: 713-651-8231



SED 0 - 31	ORM COVER SHEET
To the Honorable Commission	er of Patents and Trademarks:
To the Honorable Commission Please record the attached orig  Name of conveying party(ies): Nicholas Bachynsky	2. Name and address of receiving party(ies):
Additional name(s) of conveying party(ies) attached?	Name: Texas Pharmaceuticals, Inc.  Internal Address:
□ Yes ⊠ No	Street Address: 701 W. 4th Street
•	City: Texarkana
	State: <u>TX</u> Zip: <u>75501</u>
3. Nature of Conveyance:	·
☐ Assignment ☐ Merger	
☐ Security Agreement ☐ Change of Name	
☐ Other	Additional name(s) & address(es) attached?
Execution Date: March 4, 1998	□ Yes ⊠ No
<ol> <li>Application number(s) or patent number(s): PCT/US99         If this document is being filed together with a new apple execution date of the application is:         A. Patent Application No.(s):     </li> </ol>	B. Patent No.(s)
Additional numbers atta	
5. Name and address of party to whom correspondence concerning document should be mailed:	6. Total number of applications and patents involved:  1
Name: David L. Fox	
Internal Address: Fulbright & Jaworski LLP	7. Total fee (37 CFR 3.41): \$ 40.00
Street Address: 1301 McKinney	⊠ Enclosed
Suite 5100	☐ Authorized to be charged to deposit account
City: Houston	8. Deposit account number:
State: TX Zip: 77010-3095	(Attach duplicate copy of this page if paying by deposit account)
DO NOT US	E THIS SPACE
true copy of the original document.	nformation is true and correct and any attached copy is a
David L. Fox Name of Person Signing	Signature Date
	r chaet attachments and document

## **ASSIGNMENT**

DATE:

March 4, 1998

**ASSIGNOR:** 

NICHOLAS BACHYNSKY

701 W. 14th Street

Texarkana, Texas 75501

**ASSIGNEE:** 

TEXAS PHARMACEUTICALS, INC., a Texas corporation

701 W. 14th Street

Texarkana, Texas 75501

In consideration of Ten Dollars (\$10.00) cash in hand paid to me and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I, NICHOLAS BACHYNSKY (hereinafter called "Assignor"), who have made an invention of a novel use and method of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, assign, sell, transfer and convey to TEXAS PHARMACEUTICALS, INC., a Texas corporation, whose address is 1314 Main Street, Texarkana, Bowie County, Texas 75501 (hereinafter called "Assignee"), its successors and assigns, Assignor's entire right, title and interest in and to the following rights, interest, and property (hereinafter collectively called the "Rights"):

- 1. Assignor's invention of uses, methods and therapies of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, including without limitation Assignor's rights, powers, interests and title in and to the methods, uses and processes described in <a href="Schedule 1">Schedule 1</a> attached to this Assignment, (collectively, herein called the "Invention").
- 2. All applications for patent or like protection on said Invention that have been

or may in the future be made by Assignor or Assignor's legal representatives, in any and all countries.

- 3. All patents and like protection that have been or may in the future be granted on said Invention to Assignor or Assignor's legal representatives, in any and all countries of the world.
- 4. All substitutions for and divisions, continuations, continuations-in-part, renewals, reissues, extensions and the like of said applications and patents and similar rights or grants, including, without limitation, those obtained or permissible under past, present and future law and statutes.
- All rights of action on account of past, present and future authorized or unauthorized use of said Invention and for infringement of said patents and like protection.
- 6. The right of Assignee to file in his name disclosure documents, applications for patents and like protection for said Invention in any country and countries in the world.
- 7. All international rights of priority associated with said Invention, disclosure filings, applications, patents and like protection.

assigns forever, and Assignor does hereby bind himself, his heirs, legal representatives and assigns, to forever WARRANT and DEFEND the title to the Rights unto the said Assignee, it's successors and assigns, against any person whomsoever lawfully claiming, or to claim the same, or any part thereof.

Assignor covenants and agrees that Assignor will cooperate with Assignee such that Assignee may enjoy to the fullest extent the benefit of this Assignment. Such cooperation shall include, but not limited to, all of the following:

- 1. Assignor's prompt execution of all papers that are deemed necessary or desirable by Assignee to perfect the right, title and interest herein conveyed, and
- 2. Assignor's prompt execution of all petitions, oaths, specifications, declarations

or other papers that are deemed necessary or desirable by Assignee for filing and prosecuting patent applications, for filing and prosecuting substitute, division, continuing, or additional applications in the United States and/or all foreign countries, for filing and prosecuting applications for reissuance or reexamination of letters patent, and for interference proceedings involving and covering any of the Rights, and

3. Assignor's prompt assistance and cooperation, including but not limited to execution of documents and testifying, in the prosecution of legal proceedings involving any of the Rights, including, but not limited to, patent prosecution, interference proceedings, infringement court actions, opposition proceedings, cancellation proceedings, priority contests, unfair competition court actions, trade secret court actions, public use proceedings, slander, license breach and royalty collection proceedings and other legal proceedings.

Assignor warrants that Assignor has the right to make the assignment set forth herein and that no other person or entity has any rights of ownership or claim to the subject matter of this Assignment. This Assignment is binding upon Assignor, Assignor's heirs, administrators, executors, successors, trustees, devisees and assigns and inures to and for the benefit of Assignee, its successors and assigns.

EXECUTED effective as of the date first above written and at the time and place indicated below opposite the signature:

NICHOLAS BACHYNSKY

Date: 3/9/9

STATE OF TEXAS

COUNTY OF BEXAR

BEFORE ME, the undersigned authority, on this day personally appeared NICHOLAS BACHYNSKY known to me to be the person whose name is subscribed to the foregoing instrument, and acknowledged to me that he executed the same for the purposes and consideration therein expressed.

GIVEN UNDER MY HAND AND SEAL OF OFFICE, this the 5th day of March, 1998.

A L'ARGINIA OHLENBUSCH My commission expires May 4, 2000 Verginia Ohlenbusch

Notar Public Signature

Virginia Ohlenbusch
Notary Printed Name

Commission Expires: 5-4-2000



## **SCHEDULE 1 TO ASSIGNMENT**

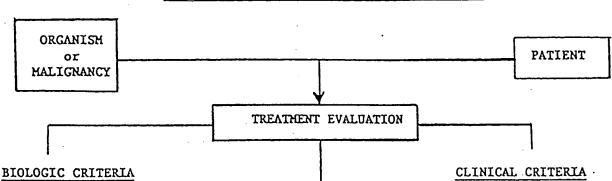
## **INVENTION**

This invention provides a medical method for: (1) prevention of life threatening hypothermia; (2) enhancing magnetic resonance spectroscopy and positron emission tomographic metabolic imaging; and (3) treatment of resistant neoplastic and infectious disease by concurrent administration of dinitrophenol [or other mitochondrial thermoregulatory uncoupling agents, e.g., carbonylcyanide m-chorophenylhydrazone (CCCP), carbonylcyanide-p-trifluoromethoxy-phenylhydrazone (FCCP), recombinant brown fat type protein, or lipid proton ionophores] and respiratory oxygen, intravenous fluids, anti-platelet drugs, as needed cooling, and specific metabolic, activating cytokines [e.g., recombinant tumor necrosis factor (TNF), interferons, etc.], hormones (e.g., glucagon), and other medications to control and focally enhance the mitochondrial uncoupling effects.

The present invention avoids the use of labor intensive, complex hyperthermia equipment, including invasive extracorporeal perfusion, with its associated thermal gradient toxicity problems to interposed normal tissues, inherent to all therapeutic methods of delivering heat from the outside-in. A new use(s)/method of generating intracellular oxygen derived free radicals, and heating from within the cell has been discovered for dinitrophenol (or other oxidative phosphorylation uncouplers) in prevention of cold injury, and treatment of free radical-thermosensitive parasites (e.g., Echinococcus), bacteria (e.g., Borrelia burgdorferi), lipid enveloped viruses (e.g., HIV), and neoplasia (e.g., gastric adenocarcinoma). It has further been discovered that cataracts, induced by dinitrophenol in the treatment of chronic obesity, can be prevented by concomitant administration of a variety of free radical scavenging agents, including tocopherol, ascorbic acid, and beta-carotene.

Briefly, the present invention is a new use(s)/method of inducing increased, intracellular free radical flux and hyperthermia, including the procedure of administrating dinitrophenol to patients in doses sufficient to denature and inactivate targeted biologic systems. Concurrent administration of tissue selective activating hormones, biologicals or drugs permits greater enhancement of the therapeutic index, while physiologic gain cooling, fluids, respiratory oxygen, and monitoring procedures permit safe therapeutic control. The figure on the attached page depicts an example use(s)/methodology of this process in an algorithm.

### SCHEMATIZED MITOCHONDRIAL UNCOUPLING METHOD MALIGNANT DISEASE FOR DIAGNOSIS ( REATMENT OF INFECTIOUS A



- \* Confirmed Diagnosis by culture, PCR, or histopathology; specific serology.
- \* Known Temperature and Heating Time required for inactivation, e.g., Treponema pallidum (syphilis)-41.5°C @ 1 hour; Borrelia burgdor-feri (Lyme Disease)-41.5°C @ 1 hour; Echinococcus multilocularis (Hydatid infestation)-41°C @ 15 minutes; HIV, chronically infected (provirus) cells (tissue culture)-42°C @ 10 hours, with recombinant TNF-a, 42°C @ 3 hours. Kaposi's sarcoma, HIV infection in the patient-42°C @ 2 hours/44°C @ 15 minutes.
- \* Unknown Temperature and Heating Time required for inactivation of meoplasms, or other infectious agents, determined by predictive - assay of biopsy/culture; generally, treatment temperature/time will be decreased due to endogenous uncoupling also occurring in targeted biologic system (except viral).

- \* History of cardiac, hepatic, pulmonary renal, CNS, malignant hyperthermia, or endocrine disease, i.e., exclusion of patients-congestive heart failure, severe dysrhythmias; alcoholic or other hepatitis with elevated bilirubin/enzymes; known endocrinopathies of brittle diabetes, pheochromocytoma, etc.; medications known to stimulate the physiologic response of hypermetabolic state and hyperthermia, e.g., vascular constrictors, anticholinergics, calcium channel blocker, etc.
- \* Pulmonary, renal, hepatic function tests; chest X-ray; CBC with platelet count; Chem profile with Ca++, Mg++, PO4=; exercisemultigated cardiac radionucleotide scan with resting ejection fraction of at least 45%, and no deterioration upon exercise.
- \* Enhancing or sensitizing agents to increase therapeutic gain, i.e., use of ionizing radiation, chemotherapy, drugs, or biologic modifiers (synergistic or additive).

METHOD PROTOCOL MANAGEMENT BASELINE & MONITORED

# TREATMENT

\* Dinitrophenol, dosage & schedule \* on "Biologic/Clinical Criteria"; IV (or IM-SC) test dose (lmg/kg) by VO2 response-lml O2/sec=20watts; common IV dosage, 1-5mg/kg, q i-4 hr, dissipation modify dose/schedule.

- \* Other mitochondrial uncoupling agents, increased potency/more localized effect, e.g., FCCP, CCCP, 6847; long chain fatty acids, and brown fat "thermogin", etc.
- \* Modulating-controlling agents, tissue specific mediators which modulate substrate turnoverrates through Krebs cycle; glucagon, .5-10mg/hr-IV; dopamine(1-10 micrograms/kg/min); insulin-dose based micrograms/kg/min); amrinone(5-7.5 serum creatinine. micrograms/kg/min); isoproterenol

- Oxygen consumption/increase, precedes core temperature increase by 4 minutes; prolonged or high risk patient-additional monitoring of tissue oxygenation by gastric pH, NMR, PET or infrared spectroscopy, ear oximetry, blood gas.
- PO 2X greater q 6-12 hr; BMR & heat \* Core temperature, esophageal, rectal, bladder catheter thermistors.
  - Cardiac function, continous display of thythm, \* Intravenous fluids, i.e., .85% Saline, rate, blood pressure and respiratory rate; Swan-Ganz catheter for high risk patient.
  - per kg /hour; observe for possible myoglobinuria urinary losses, maintain BP. and monitor fluid input/output.
  - \* Depatic function tests, at target temperature; iosoenzyme fractionation if tumor lysis is a consideration.
  - \* CNS agitation, anxiety, possible seizure prophylaxis.
- on blood glucose; dobutamine(1-15 \* Blood chemistry/electrolytes-glucose, PO4",

- Oxygen (100%) @ 4-6 liters/minute via nasal cannula/face mask.
- \* Heat control with evaporation preventing water absorbing blankets/plastic liners; cooling control-if needed with tepid H2C spray and/or fan evaporative loss; use c P.O. propylthiouracil (PTU); Decadron-I.
- D\_W = NS, supplemented with appropriate milliequivalents of K+, PO4 , Mg++; flui perfluorooctane sulfonamide, SF- \* Renal output/function, maintain at least 1-1.5ml rate to compensate for evaporative and
  - Arrhythmia control, if needed-use of nor negative inotropic, or drugs that cannot cause cardiac decompensation in hypermet bolic state e.g., lidocaine; avoidance c beta blockers and Ca++ channel blockers
  - Anxiety, possible seizure control with I.V. valium, thiopental; avoidance of drugs with acropine like effects or majo anti-psychotic drugs.

Sensitivity increased by enhanced metabolic differenc between diseased/normal tissues, i.e., 02. glucose, fat acid, ATP, phosphocreatine & specific substrate consumates. ion; lactic acid, free radical production; early diag-& predictability of disease treatment parameters/suc-

DNE-IA 6 Imgles (5X-AO<sup>5</sup>) (.5-2 micrograms/min). DIACHOSIS - Enhancement of NMR. PET. & Near-Infrared Spectroscopy. THERAPY OF INFECTIOUS & HALIGNANT DISEASE

→PARASITIC (See Illustrative Example) 41.5°C/1 hr (or less) BACTERIAL (Borrelia burgdorferi)

42°C/2 to 8 hrs (or less) ---VIRAL (HIV)

Based on predictive biopsy and use of radiation, NEOPLASTIC chemotherapy or biologic response modifiers

be determined by the specific agent treated & use of modulating, enhancing, or other combined therapy drugs.

MEDICAL USES DNP-IV @ 2-5mg/k (dosage/frequency of uncoupling agent will 93-6hr for 2x-VO

## ILLUSTRATIVE METHOD/USE EXAMPLE -

A 52 year old white Swiss male, hunting dog trainer, presented with right upper quadrant abdominal pain. History revealed past(24 month old) hepatic "cyst" surgery and treatment with albendazole(only 1 dose was given because of anaphylactic reaction). He denied history of weight loss, pulmonary, cardiac or neurologic disease. Upon physical examination, he had a weight of 198 pounds (90 Kg), height of 5'll", blood pressure 140/80, pulse-76 and regular, respirations 18/minute, and oral temperature of 37.3°C. Laboratory studies, including hepatic, renal, pulmonary and cardiac function tests were normal; complete blood count was unremarkable except for 20% eosinophilia. Ultrasound and nuclear magnetic resonance of the liver revealed 4 (2-3 cm. in diameter) cysts in the mid-right lobe; ELISA serology showed a diagnostic titer specific for Hydatid disease with Echinococcus multilocularis. The patient refused to entertain any additional surgery or albendazole therapy.

After clinical assessment and treatment evaluation, i.e., Echinococcus multilocularis protoscoleces and germinal layers are destroyed at 41°C/15 minutes, whereas liver-hepatocytes withstand temperatures of 42°C to 44°C for known periods of 20 hours and 15 minutes respectively, the patient was given 1 aspirin; 10 mg. diazepam by mouth; and, intravenous fluids of 0.85 normal saline containing 9 millimolar K<sub>2</sub>PO<sub>4</sub>, 7 milliequivalents of K<sup>+</sup>, and 2cc of 50% saturated solution of Mg<sub>2</sub>SO<sub>4</sub>/liter, were infused at a rate of 12cc/kg/hr. Urine output was maintained at 1cc/kg/hour or greater. Esophageal (optional), rectal and foley (16 gauge) tipped bladder catheter thermistors gave temperature readings every two minutes within 0.1°C. Cardiac rate, rhythm, blood pressure, and repiratory rate sensors were placed and continously displayed on a multichannel monitor. Intravenous glucagon-2mg/hr was infused, with 1 mg given prior to DNP.

The patient was covered with a water absorbing polyethelene lined blanket, and baseline respiratory gas flow/oxygen consumption (VO<sub>2</sub>) was determined using a 3 minute bag collection. Five minutes after intravenous administration of 90 mg of dinitrophenol (2% DNP/5% NaHCO<sub>3</sub> at 1 mg/kg), and determination that there was no untoward or idiosyncratic reaction, an additional 90 mg of 2,4 dinitrophenol (total of 180mg, 2mg/kg body weight) was infused. Monitored physiologic parameters are shown in the Table below. An additional VO<sub>2</sub> rate was obtained five minutes after the second dose of DNP and the patient was thereafter placed on 100% O<sub>2</sub> via nasal canula. Target core temperature was maintained by occasional exposure of a limb and/or decreasing the glucagon infusion rate to 0.25 mg/hour. After the patient was maintained at a core temperature of 41.3°C for 20 minutes, the treatment was terminated by removing the blanket and permitting evaporative and radiant heat loss to return the body temperature to a normothermic level.

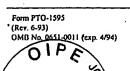
TABLE

Monitored Clinical Data On Mitochondrial Uncoupling Use/Method In Illustrative Example

(Transpart of Mydatid disease-Echinococcus multilocularis)

		(Treatment of	Hyastia aisess	e-Echinococcus mul			Other
Time (ainutes)	Hedication (type & dose)	Resp. Rate-0 (breaths/min)	Z Consumption (ml/min)	Cardiac Rate (beats/min)	Urine Output (cotal mi)	Core Temp.	(remarks)
-60	I.V. Fluids85%	18	290	78	•	37.1	Fluids @ 10-12cc per kg/hour.
-30	NS @ G.8 L/hour Glucazon-IV Drip	20	-	78	. 47	37.1	Repatic Krebs Cyclestisulation.
0	@ 2mg/hour 2.4-dinitrophenol-90=2	20	-	88	58	37.4	Covered with poly- ethylene blanker.
2	IV in 4.5ml of SINAHCO3 [prepared by dissolving 2.3cm DNP(15Z H <sub>2</sub> O) in SI NAHCO3-giving 2Z solution	24	350	. 92	-	37.8	Increased 0, con- sumption precedes temp. elevation.
5	2,4-dimitrophenol-90c; IV in 4.5ml of 5XNaHCO;	26	•	98	-	37.8	
10	Fluids increased to 1.2 L/hour; start 02	30	680	110	ıs	39.4	After VOzdeternine 1002 Oz @ 4 L/min via nasal cannula.
20		30	-	120	18	40.3	
40	Glucagon -IV Drlp	30 _	•	138	28	41.4	Lower extremity is partially exposed.
	decreased to 0.5mg/hr			140	30	41.2	Blanket removed
60	Glucagon discontinued	30		-	98	38.4	All thermistors
120	IV fluid discontinued	24	-	100	70	20.0	resoved

If Variations of the above use/method, i.e., protocol evaluation, monitoring, medications/dosages, time & temperature of mitochondrial uncoupling, will be necessitated by clinical and targeted biologic system treatment factors. Such variations for treatment of other parasitic (e.g. Halaria), bacterial (e.g., Lyne, Hansens disease), viral (e.g., HIV) and neoplastic disease will occur to those skilled in the art of medicine, and will be more fully described in the patent application.



## RECORDATION FORM COVER SHEET

Please record the attached orig	er of Patents and Trademarks: inal documents or copy thereof.
1. Chane we conveying party(ics):	2. Name and address of receiving party(ies):
Woodie Roy	Name: Texas Pharmaceuticals, Inc.
Additional name(s) of conveying party(ies) attached?	Internal Address:
□ Ycs ⊠ No	
	Street Address: 701 W. 4th Street
	City: Texarkana
	State: TX Zip: 75501
3. Nature of Conveyance:	
⊠ Assignment □ Merger	
☐ Security Agreement ☐ Change of Name	
Other	Additional name(s) & address(es) attached?
Execution Date: July 21, 1998	□ Yes ⊠ No
4. Application number(s) or patent number(s): PCT/US99/	16940
If this document is being filed together with a new appliexecution date of the application is:	cation, the
A. Patent Application No.(s):	B. Patent No.(s)
Additional numbers attached	ched? 🗆 Yes 🖾 No
5. Name and address of party to whom correspondence concerning document should be mailed:	6. Total number of applications and patents involved: 2
Name: David L. Fox	
Internal Address: Fulbright & Jaworski LLP	7. Total fee (37 CFR 3.41): \$ 40.00
Street Address: 1301 McKinney	⊠ Enclosed
Suite 5100	
City: Houston	☐ Authorized to be charged to deposit account
State: TX Zip: 77010-3095	8. Deposit account number:
	(Attach duplicate copy of this page if paying by deposit account)
DO NOT USE	THIS SPACE
9. Statement and signature.  To the best of my knowledge and belief, the foregoing infinitrue copy of the original document.  David L. Fox	17 July 2000
Name of Person Signing	Signature Date
	O

Total number of pages including cover sheet, attachments, and document.

## **ASSIGNMENT**

DATE:

July 21, 1998

**ASSIGNOR:** 

WOODIE ROY

c/o 701 W. 14th Street Texarkana, Texas 75501

**ASSIGNEE:** 

TEXAS PHARMACEUTICALS, INC., a Texas corporation

701 W. 14th Street

Texarkana, Texas 75501

In consideration of Ten Dollars (\$10.00) cash in hand paid to me and other good and valuable consideration, the receipt and sufficiency of which is hereby acknowledged, I, WOODIE ROY (hereinafter called "Assignor"), who have made an invention of a novel use and method of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, assign, sell, transfer and convey to TEXAS PHARMACEUTICALS, INC., a Texas corporation, whose address is 1314 Main Street, Texarkana, Bowie County, Texas 75501 (hereinafter called "Assignee"), its successors and assigns, Assignor's entire right, title and interest in and to the following rights, interest, and property (hereinafter collectively called the "Rights"):

1. Assignor's invention of uses, methods and therapies of inducing intracellular hyperthermia and free radical flux through the use of dinitrophenol and other mitochondrial uncoupling agents in the treatment of infectious and malignant disease, including without limitation Assignor's rights, powers, interests and title in and to the methods, uses and processes described in <a href="Schedule 1">Schedule 1</a> attached to this Assignment, (collectively, herein called the "Invention").

- 2. All applications for patent or like protection on said Invention that have been or may in the future be made by Assignor or Assignor's legal representatives, in any and all countries.
- 3. All patents and like protection that have been or may in the future be granted on said Invention to Assignor or Assignor's legal representatives, in any and all countries of the world.
- 4. All substitutions for and divisions, continuations, continuations—in—part, renewals, reissues, extensions and the like of said applications and patents and similar rights or grants, including, without limitation, those obtained or permissible under past, present and future law and statutes.
- 5. All rights of action on account of past, present and future authorized or unauthorized use of said Invention and for infringement of said patents and like protection.
- 6. The right of Assignee to file in his name disclosure documents, applications for patents and like protection for said Invention in any country and countries in the world.
- 7. All international rights of priority associated with said Invention, disclosure filings, applications, patents and like protection.

TO HAVE AND TO HOLD the Rights unto the Assignee, its successors and assigns forever, and Assignor does hereby bind himself, his heirs, legal representatives and assigns, to forever WARRANT and DEFEND the title to the Rights unto the said Assignee, its successors and assigns, against any person whomsoever lawfully claiming, or to claim the same, or any part thereof.

Assignor covenants and agrees that Assignor will cooperate with Assignee such that Assignee may enjoy to the fullest extent the benefit of this Assignment. Such cooperation shall include, but not limited to, all of the following:

1. Assignor's prompt execution of all papers that are deemed necessary or desirable by Assignee to perfect the right, title and

interest herein conveyed, and

- 2. Assignor's prompt execution of all petitions, oaths, specifications, declarations or other papers that are deemed necessary or desirable by Assignee for filing and prosecuting patent applications, for filing and prosecuting substitute, division, continuing, or additional applications in the United States and/or all foreign countries, for filing and prosecuting applications for reissuance or reexamination of letters patent, and for interference proceedings involving and covering any of the Rights, and
- 3. Assignor's prompt assistance and cooperation, including but not limited to execution of documents and testifying, in the prosecution of legal proceedings involving any of the Rights, including, but not limited to, patent prosecution, interference proceedings, infringement court actions, opposition proceedings, cancellation proceedings, priority contests, unfair competition court actions, trade secret court actions, public use proceedings, slander, license breach and royalty collection proceedings and other legal proceedings.

Assignor warrants that Assignor has the right to make the assignment set forth herein and that no other person or entity has any rights of ownership or claim to the subject matter of this Assignment as of the date of this Assignment. This Assignment is binding upon Assignor, Assignor's heirs, administrators, executors, successors, trustees, devisees and assigns and inures to and for the benefit of Assignee, its successors and assigns.

EXECUTED effective as of the date first above written and at the time and place indicated below opposite the signature:

WOODIE ROY

Date: 1-24-98

STATE OF TEXAS

COUNTY OF BOWIE

BEFORE ME, the undersigned authority, on this day personally appeared WOODIE ROY known to me to be the person whose name is subscribed to the foregoing instrument, and acknowledged to me that she executed the same for the purposes and consideration therein expressed.

GIVEN UNDER MY HAND AND SEAL OF OFFICE, this the 24th day

PATRICIA M. REYNOLDS

NOTARY PUBLIC

STATE OF TEXAS

My Commission Expires 09-09-99

Notary Public Signature

PATRICIA M. REYNOUDS

Notary Printed Name

Commission Expires: 9/9/99

## **SCHEDULE 1 TO ASSIGNMENT**

### INVENTION

This invention provides a medical method for: (1) prevention of life threatening hypothermia; (2) enhancing magnetic resonance spectroscopy and positron emission tomographic metabolic imaging; and (3) treatment of resistant neoplastic and infectious disease by concurrent administration of dinitrophenol [or other mitochondrial thermoregulatory uncoupling agents, e.g., carbonylcyanide m-chorophenylhydrazone (CCCP), carbonylcyanide-p-trifluoromethoxy-phenylhydrazone (FCCP), recombinant brown fat type protein, or lipid proton ionophores] and respiratory oxygen, intravenous fluids, anti-platelet drugs, as needed cooling, and specific metabolic, activating cytokines [e.g., recombinant tumor necrosis factor (TNF), interferons, etc.], hormones (e.g., glucagon), and other medications to control and focally enhance the mitochondrial uncoupling effects.

The present invention avoids the use of labor intensive, complex hyperthermia equipment, including invasive extracorporeal perfusion, with its associated thermal gradient toxicity problems to interposed normal tissues, inherent to all therapeutic methods of delivering heat from the outside-in. A new use(s)/method of generating intracellular oxygen derived free radicals, and heating from within the cell has been discovered for dinitrophenol (or other oxidative phosphorylation uncouplers) in prevention of cold injury, and treatment of free radical-thermosensitive parasites (e.g., Echinococcus), bacteria (e.g., Borrelia burgdorferi), lipid enveloped viruses (e.g., HIV), and neoplasia (e.g., gastric adenocarcinoma). It has further been discovered that cataracts, induced by dinitrophenol in the treatment of chronic obesity, can be prevented by concomitant administration of a variety of free radical scavenging agents, including tocopherol, ascorbic acid, and beta-carotene.

Briefly, the present invention is a new use(s)/method of inducing increased, intracellular free radical flux and hyperthermia, including the procedure of administrating dinitrophenol to patients in doses sufficient to denature and inactivate targeted biologic systems. Concurrent administration of tissue selective activating hormones, biologicals or drugs permits greater enhancement of the therapeutic index, while physiologic gain cooling, fluids, respiratory oxygen, and monitoring procedures permit safe therapeutic control. The figure on the attached page depicts an example use(s)/methodology of this process in an algorithm.

MEDICAL USES DNS-IN & S-ZaBAKE >-PARASITIC (See Illustrative Example) (dosage/frequency of 41.5°C/1 hr (or less) BACTERIAL (3orcelia burgdorferi) 93-5hr for 2x-VO, uncoupling agent will be determined by the specific agent treated 42°C/2 to 8 hrs (or less) VIRAL (HIV) & use of modulating, Based on predictive biopsy and use of radiacion. MEDFLASTIC enhancing, or other combined therapy drugs. chemotherapy or biologic response modifiers

A 52 year old white Swiss male, hunting dog trainer, presented with right upper quadrant abdominal pain. History revealed past(24 month old) hepatic "cyst" surgery and treatment with albendazole(only I dose was given because of anaphylactic reaction). He denied history of weight loss, pulmonary, cardiac or neurologic disease. Upon physical examination, he had a weight of 198 pounds (90 Kg), height of 5'll", blood pressure 140/80, pulse-76 and regular, respirations 18/minute, and oral temperature of 37.3°C. Laboratory studies, including hepatic, renal, pulmonary and cardiac function tests were normal; complete blood count was unremarkable except for 20% eosinophilia. Ultrasound and nuclear magnetic resonance of the liver revealed 4 (2-3 cm. in diameter) cysts in the mid-right lobe; ELISA serology showed a diagnostic titer specific for Hydatid disease with Echinococcus multilocularis. The patient refused to entertain any additional surgery or albendazole therapy.

After clinical assessment and treatment evaluation, i.e., Echinococcus multilocularis protoscoleces and germinal layers are destroyed at 41°C/15 minutes, whereas liver-hepatocytes withstand temperatures of 42°C to 44°C for known periods of 20 hours and 15 minutes respectively, the patient was given 1 aspirin; 10 mg. diazepam by mouth; and, intravenous fluids of 0.85 normal saline containing 9 millimolar K PO, 7 milliequivalents of K<sup>+</sup>, and 2cc of 50% saturated solution of Mg\_SO<sub>4</sub>/liter, were infused at a rate of 12cc/kg/hr. Urine output was maintained at 1cc/kg/hour or greater. Esophageal (optional), rectal and foley (16 gauge) tipped bladder catheter thermistors gave temperature readings every two minutes within 0.1°C. Cardiac rate, rhythm, blood pressure, and repiratory rate sensors were placed and continously displayed on a multichannel monitor. Intravenous glucagon-2mg/hr was infused, with 1 mg given prior to DNP.

The patient was covered with a water absorbing polyethelene lined blanket, and baseline respiratory gas flow/oxygen consumption (VO<sub>2</sub>) was determined using a 3 minute bag collection. Five minutes after intravenous administration of 90 mg of dinitrophenol (2% DNP/5% NaHCO<sub>3</sub> at 1 mg/kg), and determination that there was no untoward or idio-syncratic reaction, an additional 90 mg of 2,4 dinitrophenol (total of 180mg, 2mg/kg body weight) was infused. Monitored physiologic parameters are shown in the Table below. An additional VO<sub>2</sub> rate was obtained five minutes after the second dose of DNP and the patient was thereafter placed on 100% O<sub>2</sub> via nasal canula. Target core temperature was maintained by occasional exposure of a limb and/or decreasing the glucagon infusion rate to 0.25 mg/hour. After the patient was maintained at a core temperature of 41.3°C for 20 minutes, the treatment was terminated by removing the blanket and permitting evaporative and radiant heat loss to return the body temperature to a normothermic level.

TABLE

Monitored Clinical Data On Mitochoodrial Uncoupling Use/Method In Illustrative Example

(Treatment of Bydatid disease-Echinococcus multilocularis)

Time (minutes)	(://e & dose)	Resp. Race-0 (Sceaths/min)		Cardiac Rate (Seats/min)	Urine Output (cotal ml)	Core Temp.	Other (resurks)	
-60	f.v. fluids832 NS # 0.8 L/hour	15	290	73	•	37.1	Fluids # 10-12cc per kg/hour.	
-30	Glucagon-IV Orip 2 Zog/hour	20	-	75	47	37.1	Repatic Krebs Cycle scipulation.	
0	2,4-dimitrophenol-90mg IV in 4.5ml of SINANCO	20	-	58	53	37.4	Covered with poly- ethylene blanket.	
2	(prepared by dissolving 2.3gm DN7(131 H <sub>2</sub> 0) in 31 NaHCO <sub>1</sub> -giving 22 solution	24 =)	330	, 92	-	37.8	increased 0, con- sumption precedes temp. elevation.	
5	2.4-dimicrophenol-90cz IV in 4.3al of SINAKCO <sub>3</sub>	25	•	98	-	37.5		
10	Fluids increased to 1.2 L/hour; start Og	30	630	1:0	15	39.4	After VOzdeceralaed	
20	•	30	-	120	15	40.3	via našal cannula.	
40	Glucagon -: 7 Orly decreased to 0.3mg/hr	30	-	134	25	41.4	lover extremity is partially exposed.	
60	Glucazon discontinued	30	-	140	3¢	41.2	Blanket removed	
120	[V fluid disconcinued	24	-	100	93	38.4	All thermistors	

I/ Variations of the above use/method, i.e., protocol evaluation, monitoring, medications/dosages, time & comperature of mitochondrial uncoupling, will be necessitated by clinical and targeted biologic system treatment factors. Such variations for treatment of other parasicic (e.g. Malaria), bacterial (e.g., Lyoe, Hansens disease), viral (e.g., H(V) and neoplastic disease will occur to those skilled in the art of medicine, and will be more fully described in the patent application.

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# Exhibit 2

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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the filing date of the prior application and the national or FCT international filing date of this application.

(Application Serial No.)

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Address: Date:	701 W. 14 <sup>th</sup> Street Texarkana, Texas 75501 Q-Y-01	Name: James J-Naples Time: President